UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/063,046	05/08/2002	Abd. Al-Roof Higazi	143.006	2204

7590 10/15/2004

Rashida A. Karmali, PhD
99 Wall Street 13th Floor
New York, NY 10005

EXAMINER	
BARNHART, LORA ELIZABETH	

ART UNIT	PAPER NUMBER
1651	

DATE MAILED: 10/15/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/063,046	HIGAZI, ABD. AL-ROOF	
	Examiner	Art Unit	
	Lora E Barnhart	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 May 2002*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8* is/are pending in the application.

4a) Of the above claim(s) *3-6* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,7 and 8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 5/9/02
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I (claims 1, 2, 7 and 8) in the reply filed on 9/21/04 is acknowledged. The traversal is on the ground(s) that Groups I-IV are not patentably distinct. This is not found persuasive because said Groups I-III are drawn to unrelated compositions. Group IV is drawn to a process of use of Group I, the end point of which can be reached using compounds distinct from that of Group I.

Applicant's election with traverse of the species scuPA from a plurality of disclosed patentably distinct fibrinolytic agents in the reply filed on 9/21/04 is acknowledged. No grounds are provided for said traversal.

The requirements are still deemed proper and are therefore made FINAL.

Specification

The abstract of the disclosure is objected to because it recites material not presently elected. Correction is required. See MPEP § 608.01(b).

Applicant is reminded of the proper content of an abstract of the disclosure.

A patent abstract is a concise statement of the technical disclosure of the patent and should include that which is new in the art to which the invention pertains. If the patent is of a basic nature, the entire technical disclosure may be new in the art, and the abstract should be directed to the entire disclosure. If the patent is in the nature of an improvement in an old apparatus, process, product, or composition, the abstract should include the technical disclosure of the improvement. In certain patents, particularly those for compounds and compositions, wherein the process for making and/or the use thereof are not obvious, the abstract should set forth a process for making and/or use thereof. If the new technical disclosure involves modifications or alternatives, the abstract should mention by way of example the preferred modification or alternative.

The abstract should not refer to purported merits or speculative applications of the invention and should not compare the invention with the prior art.

Where applicable, the abstract should include the following:
(1) if a machine or apparatus, its organization and operation;
(2) if an article, its method of making;
(3) if a chemical compound, its identity and use;
(4) if a mixture, its ingredients;
(5) if a process, the steps.

Extensive mechanical and design details of apparatus should not be given.

Applicant is reminded of the proper language and format for an abstract of the disclosure.

The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

The language should be clear and concise and should not repeat information given in the title. **It should avoid using phrases which can be implied**, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc.

35 U.S.C. 112, first paragraph, requires the specification to be written in "full, clear, concise, and exact terms." The specification is replete with terms which are not clear, concise and exact. The specification should be revised carefully in order to comply with 35 U.S.C. 112, first paragraph. Examples of some unclear, inexact or verbose terms used in the specification are: "a peptide...having the property to bind at the "docking" site" (paragraph 0001); "a finger domain" (paragraph 0023); and "(the PAI-1 derived hexapeptide) **EEIMD**" (paragraphs 17, 18 and 55). Finally, the entire

specification should be reviewed carefully for spelling, grammar, and typographical errors.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 7 and 8 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands*, 858 F.2d 731, 737, 8 USPQd 1400, 1404 (Fed. Cir. 1988) (a) the breadth of the claims; (b) the nature of the invention; (c) the state of the prior art; (d) the level of one of ordinary skill; (e) the level of predictability in the art; (f) the amount of direction provided by the inventor; (g) the existence of working examples; and (h) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. While all of these factors are considered, a sufficient number are discussed below so as to create a *prima facie* case.

The breadth of claims 1 and 2 reads on a composition comprising the polypeptide EEIIMD and a fibrinolytic agent, specifically scuPA, in amounts capable of inducing fibrinolytic activity without causing hemorrhage. The breadth of claims 7 and 8

reads on a method of enhancing the fibrinolytic activity of a fibrinolytic agent, specifically scuPA, by administering the polypeptide EEIIMD and said scUPA, to induce fibrinolytic activity without causing hemorrhage.

The specification discloses a method for decreasing the vasoactivity associated with the fibrinolytic agents tPA and TNK-tPA (Example 3), but discloses no examples drawn to enhancing the fibrinolytic activity of scuPA by administering the polypeptide EEIIMD. By applicant's own admission, "the peptide of the present invention has no effect on the fibrinolytic activity of scuPA" (paragraph 30). A regimen is disclosed for coadministering alteplase with the peptide EEIIMD, but said regimen does not suggest conditions for any other plasminogen activator including scuPA (paragraphs 32, 33). The disclosure recites a preferred dosage regimen for said peptide: "an amount effective to optimally enhance the activity of the fibrinolytic activity [sic] while also preventing the harmful vasoactive effects of a fibrinolytic agent on a case by case basis" (paragraph 34). Said regimen cannot be interpreted to be applicable to scuPA, however, as applicant has explicitly stated that said peptide does not enhance the activity of scuPA. Additionally, it is not clear whether the phrase "case by case basis" refers to individual patients, diagnoses, situations, conditions, peptides or fibrinolytic agents. In any case, applicant has provided insufficient guidance for a person of ordinary skill in the art to have a reasonable expectation of success in using the claimed invention.

None of the working examples are drawn to co-administration of the EEIIMD peptide with scuPA or any uPA. While a narrow working embodiment cannot be a sole factor in determining enablement, its limited showing, in light of the unpredictable nature

of the art and the lack of direction provided by the applicant, provides additional weight to the lack of enablement in consideration of the Wands factors as a whole. Thus, one of ordinary skill in the art would not have a reasonable expectation of success in using the claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 2, 7 and 8 are rejected under 35 U.S.C. 112, second paragraph, as failing to set forth the subject matter which applicant regards as his invention. Evidence that claims fail to correspond in scope with that which applicant regards as the invention can be found in the specification and the sequence listing, submitted 3/14/02 and 9/21/04, respectively. In those papers, applicant has stated that the polypeptide of the invention has sequence **EEIIMD**, and these statements indicate that the invention is different from what is defined in the claims because the claims recite a polypeptide **EEIIMI**, a patentably distinct sequence. For the purposes of examination and sequence searching, "EEIIMI" in the claims has been interpreted to mean "EEIIMD".

Claim 1 fails to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 1 is drawn to a composition including (i.e. comprising) an **effective** amount of a polypeptide and a fibrinolytic agent to induce the **desired** level of fibrinolytic activity. Applicant provides no information in the claims or elsewhere as to what level of fibrinolytic activity might be desirable, or indeed what amount of said peptide and said agent might be appropriate. Additionally, it is not clear

from the language of the claims where or how hemorrhage might occur or be undesirable. As claim 2 depends from claim 1, claim 2 is also vague and indefinite.

Claim 7 fails to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 7 is drawn to "a method of enhancing the fibrinolytic activity of a fibrinolytic agent by administering an effective amount of the polypeptide EEIIMD and a fibrinolytic agent to induce the desired level of fibrinolytic activity without causing hemorrhage." It is not clear from the language of the claims under which conditions said polypeptide and agent are to be administered, and no process steps are provided to describe the manner in which said polypeptide and agent should be administered. Additionally, the words "effective" and "desired" fail to describe specifically what the end product of the method is. As claim 8 depends from claim 7, claim 8 is also vague and indefinite.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1, 2, 7 and 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. '143 ([A]) in view of Zhang et al. (1997, Journal of Biological Chemistry 272: 27053, [U]). The claims are drawn to a composition of the fibrinolytic agent scuPA (a form of uPA) and the peptide EEIIMD that binds it, and a method of enhancing the fibrinolytic activity of scuPA without causing hemorrhage.

U.S. '143 teaches a combination of the fibrinolytic agent uPA and low-molecular weight heparin (LMW-heparin) that binds it, and a method of co-administering uPA and LMW-heparin to dissolve blood clots while reducing the risk of hemorrhage (Example 6 and column 7, line 42 through column 9, line 35). U.S. '143 also teaches that the binding of heparin inhibits some protease activities of plasminogen activators (Figure 1). U.S. '143 does not teach the co-administration of uPA with the peptide EEIIMD.

Zhang et al. teach the peptide EEIIMD, the sequence of which is derived from the uPA regulator PAI-1. PAI-1 and the peptide EEIIMD bind to various forms of uPA (i.e. scuPA and tcuPA, p. 27053). Zhang et al. also teach that PAI-1 inhibits protease activity of plasminogen activators.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to substitute the peptide of Zhang et al. into the method and composition of U.S. '143 because said peptide, like LMW-heparin, binds to uPA, inhibits some of its protease activity, and is claimed to reduce the possibility of hemorrhage in a treated patient when co-administered with uPA. The skilled artisan would have been

motivated to make said modification for the expected benefit of increasing the safety of treating thrombic disorders with plasminogen activators.

Accordingly, one of ordinary skill in the art would have had a reasonable expectation of success in substituting the peptide of Zhang et al. into the method of U.S. '143 because said peptide is known to bind uPA and to have an effect on the activity said uPA. Similarly, the protein from which the peptide is derived, PAI-1, is well known in the art to inhibit uPA. Thus, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made.

No claims are allowed. No claims are free of the art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lora E Barnhart whose telephone number is 571-272-1928. The examiner can normally be reached on Monday-Friday, 8:00am - 4:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Lora E Barnhart

SANDRA E. SAUCIER
PRIMARY EXAMINER